

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use rosiglitazone maleate tablets safely and effectively. See full prescribing information for rosiglitazone maleate tablets.

### Rosiglitazone Maleate Tablets

Initial U.S. Approval: 1999

#### WARNING:

##### CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of rosiglitazone maleate, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone maleate must be considered.
- Rosiglitazone maleate is not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone maleate in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)
- A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone maleate to placebo, showed rosiglitazone maleate to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone maleate to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. (5.2)

#### INDICATIONS AND USAGE

Rosiglitazone tablets is a thiazolidinedione antidiabetic agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Important Limitations of Use:

- Rosiglitazone tablets should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. (1.2)
- Coadministration of rosiglitazone tablets and insulin is not recommended. (1.2, 5.3)
- Use of rosiglitazone tablets with nitrates is not recommended. (1.2, 5.2)

#### DOSAGE AND ADMINISTRATION

- Start at 4 mg daily in single or divided doses; do not exceed 8 mg daily. (2)

- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2)
- Do not initiate rosiglitazone maleate if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.4)

#### DOSAGE FORMS AND STRENGTHS

Oval film-coated tablets in the following strengths::

- 2 mg, 4 mg, and 8 mg (3)

#### CONTRAINDICATIONS

Initiation of rosiglitazone maleate in patients with established NYHA Class III or IV heart failure is contraindicated. (4)

#### WARNINGS AND PRECAUTIONS

- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.1, 5.3)
- Increased risk of myocardial ischemic events has been observed in a meta-analysis of 42 clinical trials (incidence rate 2% versus 1.5%). (5.2)
- Use of rosiglitazone maleate with nitrates is not recommended. (1.2, 5.2)
- Coadministration of rosiglitazone maleate and insulin is not recommended. (1.2, 5.3)
- Dose-related edema (5.4), weight gain (5.5), and anemia (5.9) may occur.
- Macular edema has been reported. (5.7)
- Increased incidence of bone fracture in female patients. (5.8)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with rosiglitazone maleate or any other oral antidiabetic drug (5.2)

#### ADVERSE REACTIONS

Common adverse reactions (>5%) reported in clinical trials without regard to causality were upper respiratory tract infection, injury, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact West-ward Pharmaceutical Corp, at 732-542-1191 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

#### DRUG INTERACTIONS

Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels; inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 07/2009

## FULL PRESCRIBING INFORMATION: CONTENTS \*

### WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA

#### 1 INDICATIONS AND USAGE

- 1.1 Monotherapy and Combination Therapy
- 1.2 Important Limitations of Use

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Monotherapy
- 2.2 Combination With Sulfonylurea or Metformin
- 2.3 Combination With Sulfonylurea Plus Metformin
- 2.4 Specific Patient Populations

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Cardiac Failure
- 5.2 Myocardial Ischemia
- 5.3 Congestive Heart Failure and Myocardial Ischemia During Coadministration of AVANDIA With Insulin
- 5.4 Edema
- 5.5 Weight Gain
- 5.6 Hepatic Effects
- 5.7 Macular Edema
- 5.8 Fractures
- 5.9 Hematologic Effects
- 5.10 Diabetes and Blood Glucose Control
- 5.11 Ovulation

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience
- 6.2 Laboratory Abnormalities

- 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

- 7.1 CYP2C8 Inhibitors and Inducers

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Drug-Drug Interactions

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology

#### 14 CLINICAL STUDIES

- 14.1 Monotherapy
- 14.2 Combination With Metformin or Sulfonylurea
- 14.3 Combination With Sulfonylurea Plus Metformin

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

- 17.1 Patient Advice

#### FDA-APPROVED MEDICATION GUIDE

\* Sections or subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

### WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients [see Warnings and Precautions (5.1)]. After initiation of rosiglitazone maleate, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone maleate must be considered.**
- **Rosiglitazone Maleate is not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone maleate in patients with established NYHA Class III or IV heart failure is contraindicated. [See Contraindications (4) and Warnings and Precautions (5.1).]**
- **A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone maleate to placebo, showed rosiglitazone maleate to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone maleate to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. [See Warnings and Precautions (5.2).]**

#### 1 INDICATIONS AND USAGE

##### 1.1 Monotherapy and Combination Therapy

Rosiglitazone tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

##### 1.2 Important Limitations of Use

- Due to its mechanism of action, Rosiglitazone maleate is active only in the presence of endogenous insulin. Therefore, Rosiglitazone maleate should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- The coadministration of Rosiglitazone maleate and insulin is not recommended.
- The use of Rosiglitazone maleate with nitrates is not recommended.

## 2 DOSAGE AND ADMINISTRATION

The management of antidiabetic therapy should be individualized. All patients should start rosiglitazone maleate tablets at the lowest recommended dose. Further increases in the dose of rosiglitazone maleate tablets should be accompanied by careful monitoring for adverse events related to fluid retention [see *Boxed Warning and Warnings and Precautions (5.1)* ].

Rosiglitazone maleate tablets may be administered at a starting dose of 4 mg either as a single daily dose or in 2 divided doses. For patients who respond inadequately following 8 to 12 weeks of treatment, as determined by reduction in fasting plasma glucose (FPG), the dose may be increased to 8 mg daily as monotherapy or in combination with metformin, sulfonylurea, or sulfonylurea plus metformin. Reductions in glycemic parameters by dose and regimen are described under *Clinical Studies (14.1)* . Rosiglitazone maleate tablets may be taken with or without food.

The total daily dose of rosiglitazone maleate tablets should not exceed 8 mg.

### 2.1 Monotherapy

The usual starting dose of rosiglitazone maleate tablets is 4 mg administered either as a single dose once daily or in divided doses twice daily. In clinical trials, the 4-mg twice-daily regimen resulted in the greatest reduction in FPG and hemoglobin A1c (HbA1c).

### 2.2 Combination With Sulfonylurea or Metformin

When rosiglitazone maleate tablets is added to existing therapy, the current dose(s) of the agent(s) can be continued upon initiation of therapy with rosiglitazone maleate tablets.

#### Sulfonylurea

When used in combination with sulfonylurea, the usual starting dose of Rosiglitazone maleate is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

#### Metformin

The usual starting dose of Rosiglitazone Maleate in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with Rosiglitazone Maleate.

### 2.3 Combination With Sulfonylurea Plus Metformin

The usual starting dose of rosiglitazone maleate tablets in combination with a sulfonylurea plus metformin is 4 mg administered as either a single dose once daily or divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

### 2.4 Specific Patient Populations

#### Renal Impairment

No dosage adjustment is necessary when Rosiglitazone maleate is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and Rosiglitazone maleate is also contraindicated in patients with renal impairment.

#### Hepatic Impairment

Liver enzymes should be measured prior to initiating treatment with rosiglitazone maleate. Therapy with rosiglitazone maleate should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy). After initiation of rosiglitazone maleate, liver enzymes should be monitored periodically per the clinical judgment of the healthcare professional. [See *Warnings and Precautions (5.6)* and *Clinical Pharmacology (12.3)* .]

#### Pediatric

Data are insufficient to recommend pediatric use of rosiglitazone maleate [see *Use in Specific Populations (8.4)* ].

## 3 DOSAGE FORMS AND STRENGTHS

Oval film-coated tablet contains rosiglitazone as the maleate as follows::

- 2 mg - Pink oval film coated tablets, engraved with W41.
- 4 mg - Orange oval film coated tablets, engraved with W42.
- 8 mg - Brick red oval film coated tablets, engraved with W43.

## 4 CONTRAINDICATIONS

Initiation of rosiglitazone maleate in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated [see *Boxed Warning* ].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cardiac Failure

Rosiglitazone maleate, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered [see *Boxed Warning*].

Patients with congestive heart failure (CHF) NYHA Class I and II treated with Rosiglitazone maleate have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic study was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class I or II CHF (ejection fraction  $\leq 45\%$ ) on background antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed following treatment with rosiglitazone maleate compared to placebo during the 52-week study. (See Table 1.)

Table 1. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart Failure (NYHA Class I and II) Treated With Rosiglitazone Maleate Tablets or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

Events	Rosiglitazone maleate tablets	Placebo
	N = 110 n (%)	N = 114 n (%)
<b>Adjudicated</b>		
Cardiovascular deaths	5 (5%)	4 (4%)
CHF worsening	7 (6%)	4 (4%)
– with overnight hospitalization	5 (5%)	4 (4%)
– without overnight hospitalization	2 (2%)	0 (0%)
New or worsening edema	28 (25%)	10 (9%)
New or worsening dyspnea	29 (26%)	19 (17%)
Increases in CHF medication	36 (33%)	20 (18%)
Cardiovascular hospitalization*	21 (19%)	15 (13%)
<b>Investigator-reported, non-adjudicated</b>		
Ischemic adverse events	10 (9%)	5 (4%)
– Myocardial infarction	5 (5%)	2 (2%)
– Angina	6 (5%)	3 (3%)
* Includes hospitalization for any cardiovascular reason.		

Initiation of rosiglitazone maleate in patients with established NYHA Class III or IV heart failure is contraindicated. Rosiglitazone maleate is not recommended in patients with symptomatic heart failure. [See *Boxed Warning*.]

Patients experiencing acute coronary syndromes have not been studied in controlled clinical trials. In view of the potential for development of heart failure in patients having an acute coronary event, initiation of rosiglitazone maleate is not recommended for patients experiencing an acute coronary event, and discontinuation of rosiglitazone maleate during this acute phase should be considered.

Patients with NYHA Class III and IV cardiac status (with or without CHF) have not been studied in controlled clinical trials. Rosiglitazone maleate is not recommended in patients with NYHA Class III and IV cardiac status.

## 5.2 Myocardial Ischemia

### Meta-Analysis of Myocardial Ischemia in a Group of 42 Clinical Trials

A meta-analysis was conducted retrospectively to assess cardiovascular adverse events reported across 42 double-blind, randomized, controlled clinical trials (mean duration 6 months).<sup>1</sup> These studies had been conducted to assess glucose-lowering efficacy in type 2 diabetes, and prospectively planned adjudication of cardiovascular events had not occurred in the trials. Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls. Placebo-controlled studies included monotherapy trials (Monotherapy with rosiglitazone maleate versus placebo monotherapy) and add-on trials (rosiglitazone maleate or placebo, added to sulfonylurea, metformin, or insulin). Active control studies included monotherapy trials (monotherapy with rosiglitazone maleate versus sulfonylurea or metformin monotherapy) and add-on trials (rosiglitazone maleate plus sulfonylurea or rosiglitazone maleate plus metformin, versus sulfonylurea plus metformin). A total of 14,237 patients were included (8,604 in treatment groups containing rosiglitazone maleate, 5,633 in comparator groups), with 4,143 patient-years of exposure to rosiglitazone maleate and 2,675 patient-years of exposure to comparator. Myocardial ischemic events included angina pectoris, angina pectoris aggravated, unstable angina, cardiac arrest, chest pain, coronary artery occlusion, dyspnea, myocardial infarction, coronary thrombosis, myocardial ischemia, coronary artery disease, and coronary artery disorder. In this analysis, an increased risk of myocardial ischemia with rosiglitazone maleate versus pooled comparators was observed (2% rosiglitazone maleate versus 1.5% comparators, odds ratio 1.4, 95% confidence interval [CI] 1.1, 1.8). An increased risk of myocardial ischemic events with rosiglitazone maleate was observed in the placebo-controlled studies, but not in the active-controlled studies. (See Figure 1.)

A greater increased risk of myocardial ischemic events was observed in studies where rosiglitazone maleate was added to insulin (2.8% for rosiglitazone maleate plus insulin versus 1.4% for placebo plus insulin, [OR 2.1, 95% CI 0.9, 5.1]). This increased risk reflects a difference of 3 events per 100 patient-years (95% CI -0.1, 6.3) between treatment groups. [See *Warnings and Precautions* (5.3).]

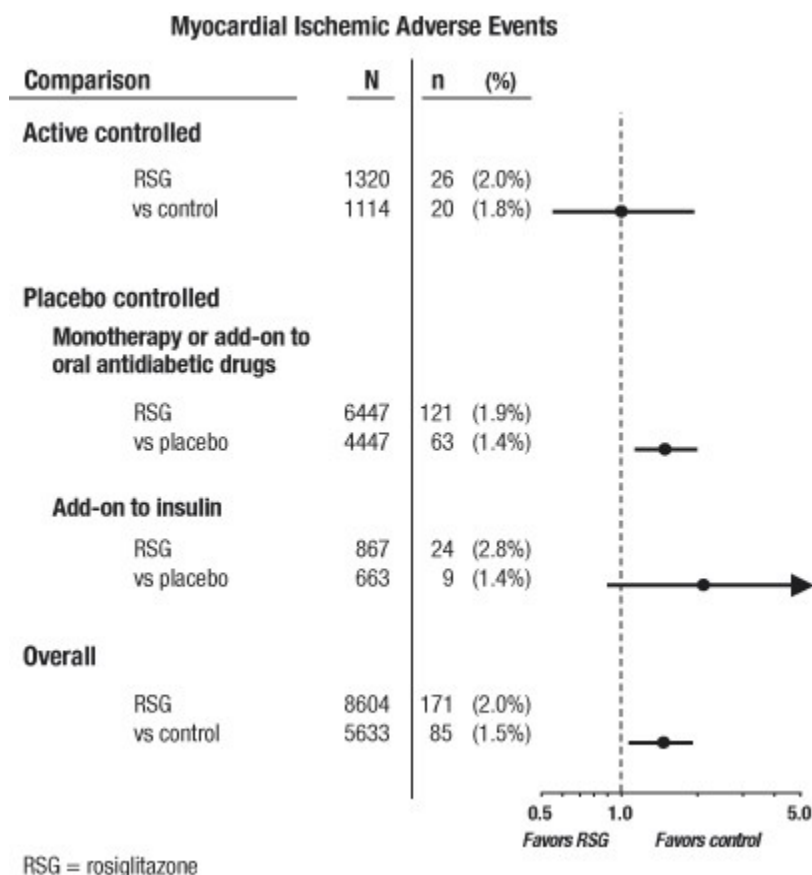


Figure 1 - Forest Plot of Odds Ratios (95% Confidence Intervals) for Myocardial Ischemic Events in the Meta-Analysis of 42 Clinical Trials

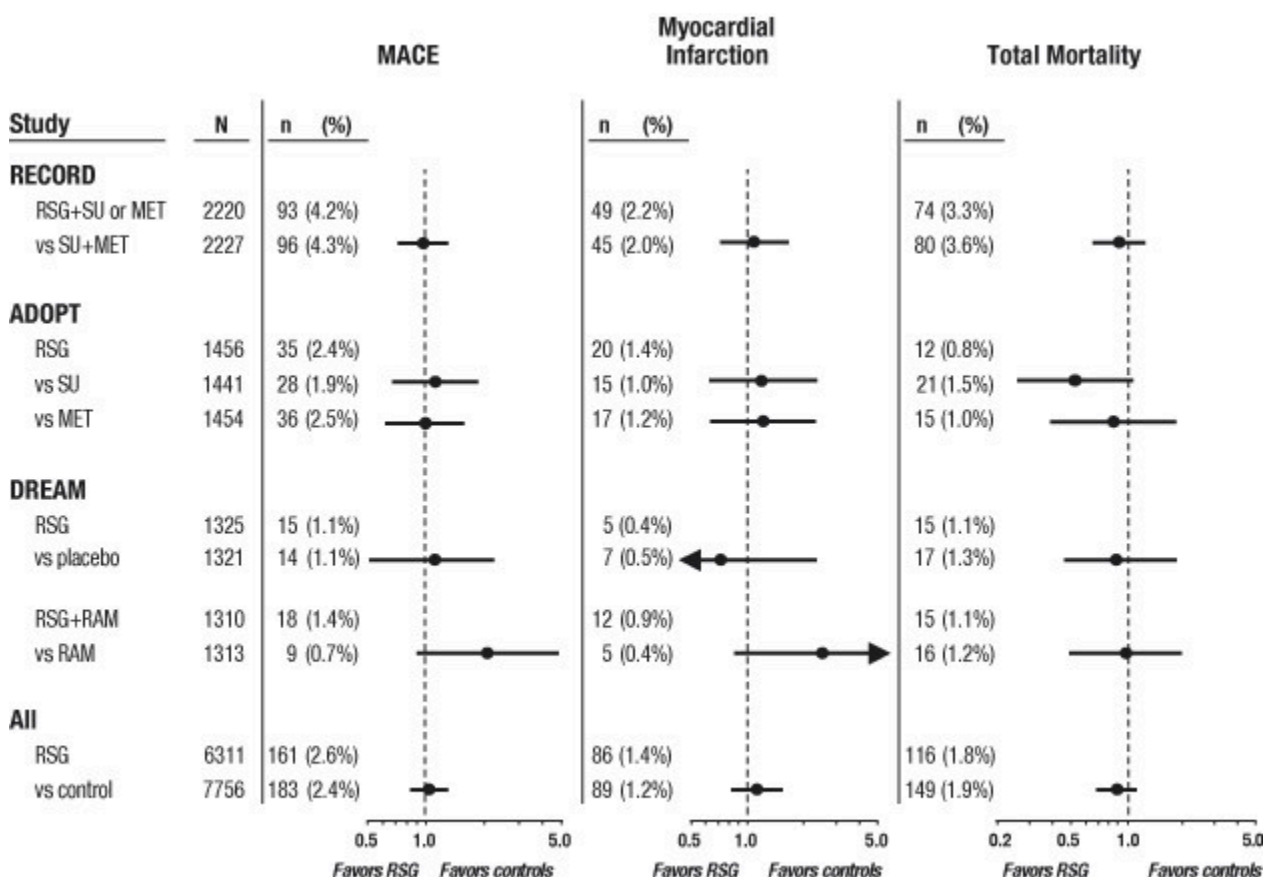
A greater increased risk of myocardial ischemia was also observed in patients who received rosiglitazone maleate and background nitrate therapy. For rosiglitazone maleate (N = 361) versus control (N = 244) in nitrate users, the odds ratio was 2.9 (95% CI 1.4, 5.9), while for non-nitrate users (about 14,000 patients total), the odds ratio was 1.3 (95% CI 0.9, 1.7). This increased risk represents a difference of 12 myocardial ischemic events per 100 patient-years (95% CI 3.3, 21.4). Most of the nitrate users had established

coronary heart disease. Among patients with known coronary heart disease who were not on nitrate therapy, an increased risk of myocardial ischemic events for rosiglitazone maleate versus comparator was not demonstrated.

### Myocardial Ischemic Events in Large Long-Term Prospective Randomized Controlled Trials of rosiglitazone maleate

Data from 3 other large, long-term, prospective, randomized, controlled clinical trials of rosiglitazone maleate were assessed separately from the meta-analysis. These 3 trials include a total of 14,067 patients (treatment groups containing rosiglitazone maleate N = 6,311, comparator groups N = 7,756), with patient-year exposure of 21,803 patient-years for rosiglitazone maleate and 25,998 patient-years for comparator. Duration of follow-up exceeded 3 years in each study. ADOPT (A Diabetes Outcomes Progression Trial) was a 4- to 6-year randomized, active-controlled study in recently diagnosed patients with type 2 diabetes naïve to drug therapy. It was an efficacy and general safety trial that was designed to examine the durability of rosiglitazone maleate as monotherapy (N = 1,456) for glycemic control in type 2 diabetes, with comparator arms of sulfonylurea monotherapy (N = 1,441) and metformin monotherapy (N = 1,454). DREAM (Diabetes Reduction Assessment with Rosiglitazone and Ramipril Medication, published report<sup>2</sup>) was a 3- to 5-year randomized, placebo-controlled study in patients with impaired glucose tolerance and/or impaired fasting glucose. It had a 2x2 factorial design, intended to evaluate the effect of rosiglitazone maleate, and separately of ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes. In DREAM, 2,635 patients were in treatment groups containing rosiglitazone maleate, and 2,634 were in treatment groups not containing rosiglitazone maleate. Interim results have been published<sup>3</sup> for RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), an ongoing open-label, 6-year cardiovascular outcomes study in patients with type 2 diabetes with an average treatment duration of 3.75 years. RECORD includes patients who have failed metformin or sulfonylurea monotherapy; those who have failed metformin are randomized to receive either add-on rosiglitazone maleate or add-on sulfonylurea, and those who have failed sulfonylurea are randomized to receive either add-on rosiglitazone maleate or add-on metformin. In RECORD, a total of 2,220 patients are receiving add-on rosiglitazone maleate, and 2,227 patients are on one of the add-on regimens not containing rosiglitazone maleate.

For these 3 trials, analyses were performed using a composite of major adverse cardiovascular events (myocardial infarction, cardiovascular death, or stroke), referred to hereafter as MACE. This endpoint differed from the meta-analysis' broad endpoint of myocardial ischemic events, more than half of which were angina. Myocardial infarction included adjudicated fatal and nonfatal myocardial infarction plus sudden death. As shown in Figure 2, the results for the 3 endpoints (MACE, MI, and Total Mortality) were not statistically significantly different between rosiglitazone maleate and comparators.



RSG = rosiglitazone; SU = sulfonylurea; MET = metformin; RAM = ramipril

Figure 2. Hazard Ratios for the Risk of MACE (Myocardial Infarction, Cardiovascular Death, or Stroke), Myocardial Infarction, and Total Mortality With Rosiglitazone Maleate Compared With a Control Group

In preliminary analyses of the DREAM trial, the incidence of cardiovascular events was higher among subjects who received rosiglitazone maleate in combination with ramipril than among subjects who received ramipril alone, as illustrated in Figure 2. This finding was not confirmed in ADOPT and RECORD (active-controlled trials in patients with diabetes) in which 30% and 40% of patients respectively, reported ACE-inhibitor use at baseline.

In their entirety, the available data on the risk of myocardial ischemia are inconclusive. Definitive conclusions regarding this risk await completion of an adequately-designed cardiovascular outcome study.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with AVANDIA or any other oral antidiabetic drug.

### 5.3 Congestive Heart Failure and Myocardial Ischemia During Coadministration of AVANDIA With Insulin

In studies in which rosiglitazone maleate was added to insulin, rosiglitazone maleate increased the risk of congestive heart failure and myocardial ischemia. (See Table 2.) Coadministration of rosiglitazone maleate and insulin is not recommended. [See *Indications and Usage (1.2) and Warnings and Precautions (5.1, 5.2)*.]

In five, 26-week, controlled, randomized, double-blind trials which were included in the meta-analysis [see *Warnings and Precautions (5.2)*], patients with type 2 diabetes mellitus were randomized to coadministration of AVANDIA and insulin (N = 867) or insulin (N = 663). In these 5 trials, rosiglitazone maleate was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 21 (2.4%) and 7 (1.1%) in the rosiglitazone maleate plus insulin and insulin groups, respectively. The total number of patients with emergent myocardial ischemia was 24 (2.8%) and 9 (1.4%) in the rosiglitazone maleate plus insulin and insulin groups, respectively (OR 2.1 [95% CI 0.9, 5.1]). Although the event rate for congestive heart failure and myocardial ischemia was low in the studied population, consistently the event rate was 2-fold or higher with coadministration of rosiglitazone maleate and insulin. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of rosiglitazone maleate. (See Table 2.)

Table 2. Occurrence of Cardiovascular Events in 5 Controlled Trials of Addition of Rosiglitazone Maleate to Established Insulin Treatment

Event*	Rosiglitazone Maleate + Insulin (n = 867) n (%)	Insulin (n = 663) n (%)
Congestive heart failure	21 (2.4%)	7 (1.1%)
Myocardial ischemia	24 (2.8%)	9 (1.4%)
Composite of cardiovascular death, myocardial infarction, or stroke	10 (1.2%)	5 (0.8%)
Stroke	5 (0.6%)	4 (0.6%)
Myocardial infarction	4 (0.5%)	1 (0.2%)
Cardiovascular death	4 (0.5%)	1 (0.2%)
All deaths	6 (0.7%)	1 (0.2%)
*Events are not exclusive; i.e., a patient with a cardiovascular death due to a myocardial infarction would be counted in 4 event categories (myocardial ischemia; cardiovascular death, myocardial infarction or stroke; myocardial infarction; cardiovascular death).		

In a sixth, 24-week, controlled, randomized, double-blind trial of rosiglitazone maleate and insulin coadministration, insulin was added to AVANDAMET<sup>®</sup> (rosiglitazone maleate and metformin HCl) (n = 161) and compared to insulin plus placebo (n = 158), after a single-blind 8-week run-in with AVANDAMET. Patients with edema requiring pharmacologic therapy and those with congestive heart failure were excluded at baseline and during the run-in period. In the group receiving AVANDAMET plus insulin, there was one

myocardial ischemic event and one sudden death. No myocardial ischemia was observed in the insulin group, and no congestive heart failure was reported in either treatment group.

#### 5.4 Edema

Rosiglitazone maleate should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg of rosiglitazone maleate once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, rosiglitazone maleate should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure [see *Boxed Warning*, *Warnings and Precautions* (5.1), and *Patient Counseling Information* (17.1)]. In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone maleate, and may be dose related. Patients with ongoing edema were more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone maleate [see *Adverse Reactions* (6.1)].

#### 5.5 Weight Gain

Dose-related weight gain was seen with rosiglitazone maleate alone and in combination with other hypoglycemic agents (Table 3).

The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure [see *Boxed Warning*].

Table 3. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials

		<b>Control Group</b>		<b>Rosiglitazone maleate 4 mg</b>	<b>Rosiglitazone maleate 8 mg</b>
<b>Monotherapy</b>	<b>Duration</b>		<b>Median (25<sup>th</sup>, 75<sup>th</sup> percentile)</b>	<b>Median (25<sup>th</sup>, 75<sup>th</sup> percentile)</b>	<b>Median (25<sup>th</sup>, 75<sup>th</sup> percentile)</b>
	26 weeks	placebo	-0.9 (-2.8, 0.9) n = 210	1.0 (-0.9, 3.6) n = 436	3.1 (1.1, 5.8) n = 439
	52 weeks	sulfonylurea	2.0 (0, 4.0) n = 173	2.0 (-0.6, 4.0) n = 150	2.6 (0, 5.3) n = 157
<b>Combination therapy</b>					
Sulfonylurea	24-26 weeks	sulfonylurea	0 (-1.0, 1.3) n = 1,155	2.2 (0.5, 4.0) n = 613	3.5 (1.4, 5.9) n = 841
Metformin	26 weeks	metformin	-1.4 (-3.2, 0.2) n = 175	0.8 (-1.0, 2.6) n = 100	2.1 (0, 4.3) n = 184
Insulin	26 weeks	insulin	0.9 (-0.5, 2.7) n = 162	4.1 (1.4, 6.3) n = 164	5.4 (3.4, 7.3) n = 150
Sulfonylurea + metformin	26 weeks	sulfonylurea + metformin	0.2 (-1.2, 1.6) n = 272	2.5 (0.8, 4.6) n = 275	4.5 (2.4, 7.3) n = 276

In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed with type 2 diabetes not previously treated with antidiabetic medication [see *Clinical Studies* (14.1)], the median weight change (25<sup>th</sup>, 75<sup>th</sup> percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for rosiglitazone maleate, 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

In a 24-week study in pediatric patients aged 10 to 17 years treated with rosiglitazone maleate 4 to 8 mg daily, a median weight gain of 2.8 kg (25<sup>th</sup>, 75<sup>th</sup> percentiles: 0.0, 5.8) was reported.



## 5.6 Hepatic Effects

Liver enzymes should be measured prior to the initiation of therapy with rosiglitazone maleate in all patients and periodically thereafter per the clinical judgment of the healthcare professional. Therapy with rosiglitazone maleate should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with rosiglitazone maleate should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with rosiglitazone maleate in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with rosiglitazone maleate, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with rosiglitazone maleate should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with rosiglitazone maleate should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued. [See *Adverse Reactions* (6.2, 6.3).]

## 5.7 Macular Edema

Macular edema has been reported in postmarketing experience in some diabetic patients who were taking rosiglitazone maleate or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. [See *Adverse Reactions* (6.1).]

## 5.8 Fractures

In a 4- to 6-year comparative study (ADOPT) of glycemic control with monotherapy in drug-naïve patients recently diagnosed with type 2 diabetes mellitus, an increased incidence of bone fracture was noted in female patients taking rosiglitazone maleate. Over the 4- to 6-year period, the incidence of bone fracture in females was 9.3% (60/645) for rosiglitazone maleate versus 3.5% (21/605) for glyburide and 5.1% (30/590) for metformin. This increased incidence was noted after the first year of treatment and persisted during the course of the study. The majority of the fractures in the women who received rosiglitazone maleate occurred in the upper arm, hand, and foot. These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). No increase in fracture rates was observed in men treated with rosiglitazone maleate. The risk of fracture should be considered in the care of patients, especially female patients, treated with rosiglitazone maleate, and attention given to assessing and maintaining bone health according to current standards of care.

## 5.9 Hematologic Effects

Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with rosiglitazone maleate [see *Adverse Reactions* (6.2)]. The observed changes may be related to the increased plasma volume observed with treatment with rosiglitazone maleate.

## 5.10 Diabetes and Blood Glucose Control

Patients receiving rosiglitazone maleate in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response.

## 5.11 Ovulation

Therapy with rosiglitazone maleate, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking rosiglitazone maleate [see *Use in Specific Populations* (8.1)]. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies; therefore, the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies [see *Nonclinical Toxicology* (13.1)], the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with rosiglitazone maleate should be reviewed.

# 6 ADVERSE REACTIONS

## 6.1 Clinical Trial Experience

### Adult

In clinical trials, approximately 9,900 patients with type 2 diabetes have been treated with rosiglitazone maleate.

Short-Term Trials of Rosiglitazone Maleate as Monotherapy and in Combination With Other Hypoglycemic Agents  
The incidence and types of adverse events reported in short-term clinical trials of rosiglitazone maleate as monotherapy are shown in Table 4.

Table 4. Adverse Events ( $\geq 5\%$  in Any Treatment Group) Reported by Patients in Short-Term\* Double-Blind Clinical Trials With Rosiglitazone Maleate as Monotherapy

Preferred Term	Rosiglitazone maleate Monotherapy	Placebo	Metformin	Sulfonylureas <sup>†</sup>
	N = 2,526	N = 601	N = 225	N = 626
	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9

\* Short-term trials ranged from 8 weeks to 1 year.

<sup>†</sup> Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).

Overall, the types of adverse reactions without regard to causality reported when rosiglitazone maleate was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with rosiglitazone maleate.

Events of anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with rosiglitazone maleate.

In double-blind studies, anemia was reported in 1.9% of patients receiving rosiglitazone maleate as monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin. Reports of anemia were greater in patients treated with a combination of AVANDIA and metformin (7.1%) and with a combination of AVANDIA and a sulfonylurea plus metformin (6.7%) compared to monotherapy with Arosiglitazone maleate or in combination with a sulfonylurea (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies [see *Adverse Reactions* (6.2)].

In clinical trials, edema was reported in 4.8% of patients receiving rosiglitazone maleate as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The reporting rate of edema was higher for rosiglitazone maleate 8 mg in sulfonylurea combinations (12.4%) compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of patients receiving rosiglitazone maleate in the insulin combination trials compared to 5.4% on insulin alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with rosiglitazone maleate [see *Boxed Warning and Warnings and Precautions* (5.3)].

In controlled combination therapy studies with sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for rosiglitazone maleate plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by capillary blood glucose concentration  $\leq 50$  mg/dL, were 6% for insulin alone and 12% (4 mg) and 14% (8 mg) for insulin in combination with rosiglitazone maleate. [See *Warnings and Precautions* (5.10).]

#### *Long-Term Trial of Rosiglitazone Maleate as Monotherapy*

A 4- to 6-year study (ADOPT) compared the use of rosiglitazone maleate (n = 1,456), glyburide (n = 1,441), and metformin (n = 1,454) as monotherapy in patients recently diagnosed with type 2 diabetes who were not previously treated with antidiabetic medication. Table 5 presents adverse reactions without regard to causality; rates are expressed per 100 patient-years (PY) exposure to account for the differences in exposure to study medication across the 3 treatment groups.

In ADOPT, fractures were reported in a greater number of women treated with rosiglitazone maleate (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who received rosiglitazone were reported in the upper arm, hand, and foot. [See *Warnings and Precautions* (5.7).] The observed incidence of fractures for male patients was similar among the 3 treatment groups.

Table 5. On-Therapy Adverse Events ( $\geq 5$  Events/100 Patient-Years [PY]) in Any Treatment Group Reported in a 4- to 6-Year Clinical Trial of Rosiglitazone Maleate as Monotherapy (ADOPT)

	<b>Rosiglitazone Maleate</b>	<b>Glyburide</b>	<b>Metformin</b>
	<b>N = 1,456</b>	<b>N = 1,441</b>	<b>N = 1,454</b>
	<b>PY = 4,954</b>	<b>PY = 4,244</b>	<b>PY = 4,906</b>
Nasopharyngitis	6.3	6.9	6.6
Back pain	5.1	4.9	5.3
Arthralgia	5.0	4.8	4.2
Hypertension	4.4	6.0	6.1
Upper respiratory tract infection	4.3	5.0	4.7

Hypoglycemia	2.9	13.0	3.4
Diarrhea	2.5	3.2	6.8

### **Pediatric**

Rosiglitazone maleate has been evaluated for safety in a single, active-controlled trial of pediatric patients with type 2 diabetes in which 99 were treated with rosiglitazone maleate and 101 were treated with metformin. The most common adverse reactions (>10%) without regard to causality for either rosiglitazone maleate or metformin were headache (17% versus 14%), nausea (4% versus 11%), nasopharyngitis (3% versus 12%), and diarrhea (1% versus 13%). In this study, one case of diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in the rosiglitazone group who had FPG of #300 mg/dL, 2+ ketonuria, and an elevated anion gap.

## **6.2 Laboratory Abnormalities**

### **Hematologic**

Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with AVANDIA (mean decreases in individual studies as much as 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily during the first 3 months following initiation of therapy with AVANDIA or following a dose increase in AVANDIA. The time course and magnitude of decreases were similar in patients treated with a combination of AVANDIA and other hypoglycemic agents or monotherapy with AVANDIA. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. In a single study in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL and 0.95%, respectively) were reported. Small decreases in hemoglobin and hematocrit have also been reported in pediatric patients treated with AVANDIA. White blood cell counts also decreased slightly in adult patients treated with AVANDIA. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with AVANDIA.

### **Lipids**

Changes in serum lipids have been observed following treatment with rosiglitazone maleate in adults [*see Clinical Pharmacology (12.2)*]. Small changes in serum lipid parameters were reported in children treated with rosiglitazone maleate for 24 weeks.

### **Serum Transaminase Levels**

In pre-approval clinical studies in 4,598 patients treated with rosiglitazone maleate (3,600 patient-years of exposure) and in a long-term 4- to 6-year study in 1,456 patients treated with rosiglitazone maleate (4,954 patient-years exposure), there was no evidence of drug-induced hepatotoxicity.

In pre-approval controlled trials, 0.2% of patients treated with rosiglitazone maleate had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone maleate were reversible. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone maleate compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. [*See Warnings and Precautions (5.6).*]

In the 4- to 6-year ADOPT trial, patients treated with rosiglitazone maleate (4,954 patient-years exposure), glyburide (4,244 patient-years exposure), or metformin (4,906 patient-years exposure), as monotherapy, had the same rate of ALT increase to >3X upper limit of normal (0.3 per 100 patient-years exposure).

## **6.3 Postmarketing Experience**

In addition to adverse reactions reported from clinical trials, the events described below have been identified during post-approval use of rosiglitazone maleate. Because these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

In patients receiving thiazolidinedione therapy, serious adverse events with or without a fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported [*see Boxed Warning and Warnings and Precautions (5.1)*].

There are postmarketing reports with rosiglitazone maleate of hepatitis, hepatic enzyme elevations to 3 or more times the upper limit of normal, and hepatic failure with and without fatal outcome, although causality has not been established.

Rash, pruritus, urticaria, angioedema, anaphylactic reaction, and Stevens-Johnson syndrome have been reported rarely.

Reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received [see *Warnings and Precautions* (5.7)].

## 7 DRUG INTERACTIONS

### 7.1 CYP2C8 Inhibitors and Inducers

An inhibitor of CYP2C8 (e.g., gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (e.g., rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. [See *Clinical Pharmacology* (12.4).]

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C.

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Careful monitoring of glucose control is essential in such patients. Most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

### Human Data

Rosiglitazone has been reported to cross the human placenta and be detectable in fetal tissue. The clinical significance of these findings is unknown. There are no adequate and well-controlled studies in pregnant women. rosiglitazone maleate should not be used during pregnancy.

### Animal Studies

There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

### 8.2 Labor and Delivery

The effect of rosiglitazone on labor and delivery in humans is not known.

### 8.3 Nursing Mothers

Drug-related material was detected in milk from lactating rats. It is not known whether rosiglitazone maleate is excreted in human milk. Because many drugs are excreted in human milk, rosiglitazone maleate should not be administered to a nursing woman.

### 8.4 Pediatric Use

After placebo run-in including diet counseling, children with type 2 diabetes mellitus, aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m<sup>2</sup>, were randomized to treatment with 2 mg twice daily of rosiglitazone maleate (n = 99) or 500 mg twice daily of metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, FPG decreased in patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of treatment, 49% of patients treated with rosiglitazone maleate and 55% of metformin-treated patients had their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at week 24, the mean change from baseline in HbA1c was -0.14% with rosiglitazone maleate and -0.49% with metformin. There was an insufficient number of patients in this study to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic therapy (Table 6).

Table 6. Week 24 FPG and HbA1c Change From Baseline Last-Observation-Carried Forward in Children With Baseline HbA1c >6.5%

	Naïve Patients		Previously-Treated Patients	
	Metformin	Rosiglitazone	Metformin	Rosiglitazone

	N = 40	N = 45	N = 43	N = 32
<b>FPG (mg/dL)</b>				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted treatment difference* (rosiglitazone–metformin) <sup>†</sup> (95% CI)		8 (-15, 30)		21 (-9, 51)
% of patients with ≥30 mg/dL decrease from baseline	43%	27%	44%	28%
<b>HbA1c (%)</b>				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted treatment difference* (rosiglitazone–metformin) <sup>†</sup> (95% CI)		0.2 (-0.6, 0.9)		0.5 (-0.2, 1.3)
% of patients with ≥0.7% decrease from baseline	63%	52%	54%	31%
* Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.				
<sup>†</sup> Positive values for the difference favor metformin.				

Treatment differences depended on baseline BMI or weight such that the effects of rosiglitazone maleate and metformin appeared more closely comparable among heavier patients. The median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin [see *Warnings and Precautions* (5.4) ]. Fifty-four percent of patients treated with rosiglitazone and 32% of patients treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of patients treated with metformin gained ≥5 kg on study.

Adverse events observed in this study are described in *Adverse Reactions* (6.1 ).

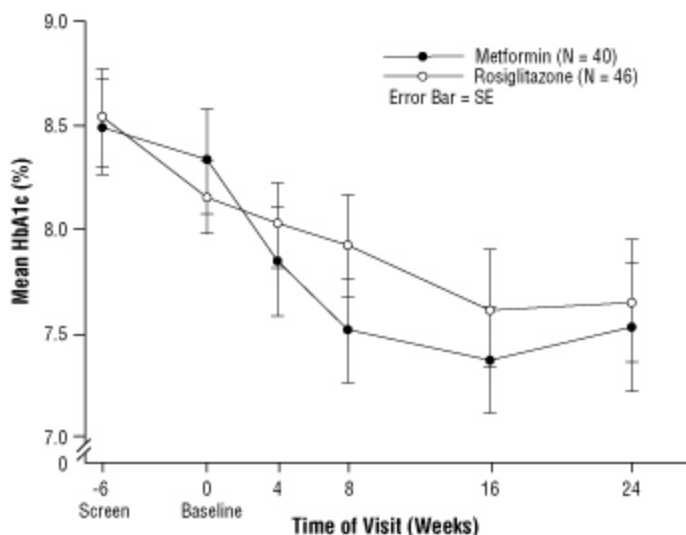


Figure 3. Mean HbA1c Over Time in a 24-Week Study of Rosiglitazone Maleate and Metformin in Pediatric Patients — Drug-Naïve Subgroup

### 8.5 Geriatric Use

Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone [see *Clinical Pharmacology* (12.3)]. Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older ( $\geq 65$  years) and younger ( $< 65$  years) patients were observed.

## 10 OVERDOSAGE

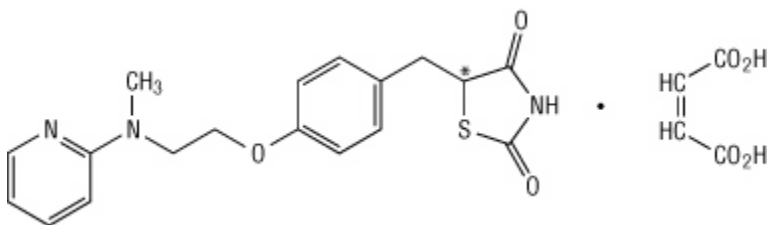
Limited data are available with regard to overdosage in humans. In clinical studies in volunteers, rosiglitazone maleate has been administered at single oral doses of up to 20 mg and was well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

## 11 DESCRIPTION

Rosiglitazone maleate is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. Rosiglitazone maleate improves glycemic control while reducing circulating insulin levels.

Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

Chemically, rosiglitazone maleate is ( $\pm$ )-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The structural formula of rosiglitazone maleate is:



### Structural Formula

The molecular formula is  $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$ . Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range. Each film-coated tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg or 8 mg, for oral administration.

Inactive ingredients are: Lactose monohydrate, lechithinm, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3350, polyvinyl alcohol, red iron oxide, sodium starch glycolate type A, talc, titanium dioxide. The 4 mg tablet also contains FD&C yellow No. 6 aluminum lake and yellow iron oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR $\gamma$  nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPAR $\gamma$ -responsive genes also participate in the regulation of fatty acid metabolism. Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, the antidiabetic activity of rosiglitazone was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. Pharmacological studies in animal models indicate that rosiglitazone inhibits hepatic gluconeogenesis. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

### 12.2 Pharmacodynamics

Patients with lipid abnormalities were not excluded from clinical trials of Rosiglitazone maleate. In all 26-week controlled trials, across the recommended dose range, rosiglitazone maleate as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls (Table 7).

Increases in LDL occurred primarily during the first 1 to 2 months of therapy with rosiglitazone maleate and LDL levels remained elevated above baseline throughout the trials. In contrast, HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of therapy and then appeared to decrease over time. Because of the temporal nature of lipid changes, the 52-week glyburide-controlled study is most pertinent to assess long-term effects on lipids. At baseline, week 26, and week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0, respectively, for rosiglitazone maleate 4 mg twice daily. The corresponding values for glyburide were 3.2, 3.1, and 2.9. The differences in change from baseline between rosiglitazone maleate and glyburide at week 52 were statistically significant.

The pattern of LDL and HDL changes following therapy with rosiglitazone maleate in combination with other hypoglycemic agents were generally similar to those seen with rosiglitazone maleate in monotherapy.

The changes in triglycerides during therapy with rosiglitazone maleate were variable and were generally not statistically different from placebo or glyburide controls.

Table 7. Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week Glyburide-Controlled Monotherapy Studies

	Placebo-Controlled Studies Week 26			Glyburide-Controlled Study Week 26 and Week 52			
	Placebo	Rosiglitazone maleate		Glyburide Titration		Rosiglitazone maleate 8 mg	
		4 mg daily *	8 mg daily *	Wk 26	Wk 52	Wk 26	Wk 52
<b>Free fatty acids</b>							
N	207	428	436	181	168	166	145
Baseline (mean)	18.1	17.5	17.9	26.4	26.4	26.9	26.6
% Change from baseline (mean)	+0.2%	-7.8%	-14.7%	-2.4%	-4.7%	-20.8%	-21.5%
<b>LDL</b>							
N	190	400	374	175	160	161	133



Baseline (mean)	123.7	126.8	125.3	142.7	141.9	142.1	142.1
% Change from baseline (mean)	+4.8%	+14.1%	+18.6%	-0.9%	-0.5%	+11.9%	+12.1%
<b>HDL</b>							
N	208	429	436	184	170	170	145
Baseline (mean)	44.1	44.4	43.0	47.2	47.7	48.4	48.3
% Change from baseline (mean)	+8.0%	+11.4%	+14.2%	+4.3%	+8.7%	+14.0%	+18.5%
* Once daily and twice daily dosing groups were combined.							

### 12.3 Pharmacokinetics

Maximum plasma concentration ( $C_{\max}$ ) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 8). The elimination half-life is 3 to 4 hours and is independent of dose.

Table 8. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (N = 32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
AUC <sub>0-inf</sub> [ng•hr/mL]	358 (112)	733 (184)	2,971 (730)	2,890 (795)
$C_{\max}$ [ng/mL]	76 (13)	156 (42)	598 (117)	432 (92)
Half-life [hr]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F* [L/hr]	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)
* CL/F = Oral clearance.				

### Absorption

The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing.

Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease in  $C_{\max}$  and a delay in  $T_{\max}$  (1.75 hours). These changes are not likely to be clinically significant; therefore, rosiglitazone maleate may be administered with or without food.

## **Distribution**

The mean (CV%) oral volume of distribution ( $V_{ss}/F$ ) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

## **Metabolism**

Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone.

In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

## **Excretion**

Following oral or intravenous administration of [ $^{14}\text{C}$ ]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [ $^{14}\text{C}$ ]related material ranged from 103 to 158 hours.

## **Population Pharmacokinetics in Patients with Type 2 Diabetes**

Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance ( $CL/F$ ) and oral steady-state volume of distribution ( $V_{ss}/F$ ) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted  $CL/F$  and  $V_{ss}/F$  values varied by <1.7-fold and <2.3-fold, respectively. Additionally, rosiglitazone  $CL/F$  was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

## **Special Populations**

### **Geriatric**

Results of the population pharmacokinetic analysis ( $n = 716 < 65$  years;  $n = 331 \geq 65$  years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

### **Gender**

Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients ( $n = 405$ ) was approximately 6% lower compared to male patients of the same body weight ( $n = 642$ ).

As monotherapy and in combination with metformin, rosiglitazone maleate improved glycemic control in both males and females. In metformin combination studies, efficacy was demonstrated with no gender differences in glycemic response.

In monotherapy studies, a greater therapeutic response was observed in females; however, in more obese patients, gender differences were less evident. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target  $\text{PPAR}_{\gamma}$  is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to rosiglitazone maleate in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

### **Hepatic Impairment**

Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound  $C_{\max}$  and  $\text{AUC}_{0-\infty}$  were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Therapy with rosiglitazone maleate should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels ( $\text{ALT} > 2.5\times$  upper limit of normal) at baseline [see *Warnings and Precautions* (5.6)].

### **Pediatric**

Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging from 10 to 17 years (weights ranging from 35 to 178.3 kg). Population mean  $CL/F$  and  $V/F$  of rosiglitazone were 3.15 L/hr and 13.5 L, respectively. These estimates of  $CL/F$  and  $V/F$  were consistent with the typical parameter estimates from a prior adult population analysis.

### **Renal Impairment**

There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in

such patients receiving rosiglitazone maleate. Since metformin is contraindicated in patients with renal impairment, coadministration of metformin with rosiglitazone maleate is contraindicated in these patients.

### **Race**

Results of a population pharmacokinetic analysis including subjects of Caucasian, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

## **12.4 Drug-Drug Interactions**

### **Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P450**

In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. rosiglitazone maleate (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4.

### ***Gemfibrozil***

Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced [*see Drug Interactions (7.1)*].

### ***Rifampin***

Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of rosiglitazone (8 mg) alone [*see Drug Interactions (7.1)*].<sup>4</sup>

### **Glyburide**

Rosiglitazone maleate (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone maleate (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C<sub>max</sub> of approximately 30%. In Japanese subjects, glyburide AUC and C<sub>max</sub> slightly increased following coadministration of rosiglitazone maleate.

### **Glimepiride**

Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of rosiglitazone maleate. No clinically significant reductions in glimepiride AUC and C<sub>max</sub> were observed after repeat doses of rosiglitazone maleate (8 mg once daily) for 8 days in healthy adult subjects.

### **Metformin**

Concurrent administration of rosiglitazone maleate (2 mg twice daily) and metformin (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state pharmacokinetics of either metformin or rosiglitazone.

### **Acarbose**

Coadministration of acarbose (100 mg three times daily) for 7 days in healthy volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of rosiglitazone maleate.

### **Digoxin**

Repeat oral dosing of rosiglitazone maleate (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

### **Warfarin**

Repeat dosing with rosiglitazone maleate had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

### **Ethanol**

A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with rosiglitazone maleate.

### **Ranitidine**

Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the pharmacokinetics of either single oral or intravenous doses of rosiglitazone in healthy volunteers. These results suggest that the absorption of oral rosiglitazone is not altered in conditions accompanied by increases in gastrointestinal pH.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses  $\geq 1.5$  mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses  $\geq 0.3$  mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

#### Mutagenesis

Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic activation.

#### Impairment of Fertility

Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended human daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

### 13.2 Animal Toxicology

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

## 14 CLINICAL STUDIES

### 14.1 Monotherapy

#### Short Term Clinical Studies

A total of 2,315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with rosiglitazone maleate as monotherapy in 6 double-blind studies, which included two 26-week placebo-controlled studies, one 52-week glyburide-controlled study, and 3 placebo-controlled dose-ranging studies of 8 to 12 weeks duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week placebo run-in period prior to randomization.

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes ( $n = 1,401$ ) with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL [101 to 425 mg/dL] and mean baseline HbA1c 8.9% [5.2% to 16.2%]), were conducted. Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c compared to baseline and relative to placebo. Data from one of these studies are summarized in Table 9.

Table 9. Glycemic Parameters in a 26-Week Placebo-Controlled Trial

	Placebo	Rosiglitazone maleate		Rosiglitazone maleate	
		4 mg once daily	2 mg twice daily	8 mg once daily	4 mg twice daily

	N = 173	N = 180	N = 186	N = 181	N = 187
<b>FPG (mg/dL)</b>					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	–	-31*	-43*	-49*	-62*
% of patients with $\geq 30$ mg/dL decrease from baseline	19%	45%	54%	58%	70%
<b>HbA1c (%)</b>					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference from placebo (adjusted mean)	–	-0.8*	-0.9*	-1.1*	-1.5*
% of patients with $\geq 0.7\%$ decrease from baseline	9%	28%	29%	39%	54%
*p<0.0001 compared to placebo.					

When administered at the same total daily dose, rosiglitazone maleate was generally more effective in reducing FPG and HbA1c when administered in divided doses twice daily compared to once daily doses. However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice daily doses was not statistically significant.

#### Long Term Clinical Studies

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were randomized to treatment with rosiglitazone maleate 2 mg twice daily (N = 195) or rosiglitazone maleate 4 mg twice daily (N = 189) or glyburide (N = 202) for 52 weeks. Patients receiving glyburide were given an initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in 2.5 mg/day increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize glycemic control. Thereafter the glyburide dose was kept constant.

The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (Figure 4 and Figure 5). At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/

dL and -0.53% with rosiglitazone maleate 4 mg twice daily; -25.4 mg/dL and -0.27% with rosiglitazone maleate 2 mg twice daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between rosiglitazone maleate 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with rosiglitazone maleate; however, this effect was less durable over time. The improvement in glycemic control seen with rosiglitazone maleate 4 mg twice daily at week 26 was maintained through week 52 of the study.

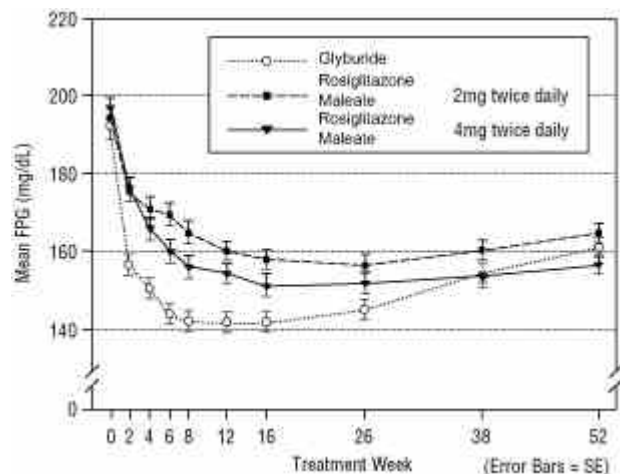


Figure 4 Mean FPG Over Time in a 52-Week Glyburide-Controlled Study

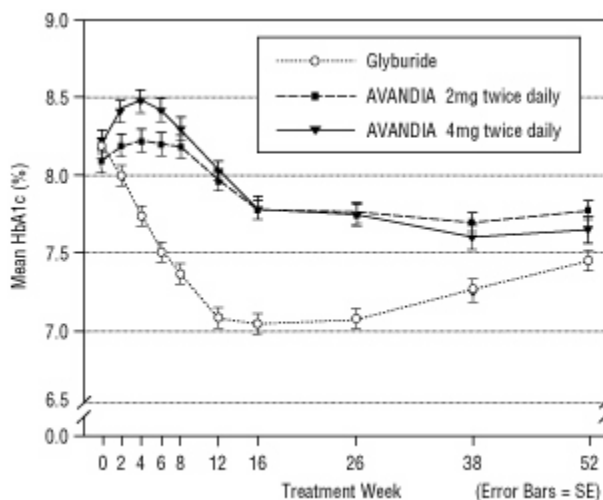


Figure 5 Mean HbA1c Over Time in a 52 Week-Glyburide-Controlled Study

Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5% (2 mg twice daily) and 1.6% (4 mg twice daily) of patients treated with rosiglitazone maleate. The improvements in glycemic control were associated with a mean weight gain of 1.75 kg and 2.95 kg for patients treated with 2 mg and 4 mg twice daily of rosiglitazone maleate, respectively, versus 1.9 kg in glyburide-treated patients. In patients treated with rosiglitazone maleate, C-peptide, insulin, pro-insulin, and pro-insulin split products were significantly reduced in a dose-ordered fashion, compared to an increase in the glyburide-treated patients.

A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind, controlled trial (n = 4,351) conducted over 4 to 6 years to compare the safety and efficacy of rosiglitazone maleate, metformin, and glyburide monotherapy in patients recently diagnosed with type 2 diabetes mellitus ( $\leq 3$  years) inadequately controlled with diet and exercise. The mean age of patients in this trial was 57 years and the majority of patients (83%) had no known history of cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%, respectively. Patients were randomized to receive either rosiglitazone maleate 4 mg once daily, glyburide 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic control up to a maximum of 4 mg twice daily for rosiglitazone maleate, 7.5 mg twice daily for glyburide, and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive FPG  $> 180$  mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study medication or time to inadequate glycemic control, as determined by an independent adjudication committee.

The cumulative incidence of the primary efficacy outcome at 5 years was 15% with rosiglitazone maleate, 21% with metformin, and 34% with glyburide (hazard ratio 0.68 [95% CI 0.55, 0.85] versus metformin, HR 0.37 [95% CI 0.30, 0.45] versus glyburide).

Cardiovascular and adverse event data (including effects on body weight and bone fracture) from ADOPT for rosiglitazone maleate, metformin, and glyburide are described in Warnings and Precautions (5.2, 5.5, and 5.8) and Adverse Reactions (6.1), respectively. As with all medications, efficacy results must be considered together with safety information to assess the potential benefit and risk for an individual patient.

## 14.2 Combination With Metformin or Sulfonylurea

The addition of rosiglitazone maleate to either metformin or sulfonylurea resulted in significant reductions in hyperglycemia compared to either of these agents alone. These results are consistent with an additive effect on glycemic control when rosiglitazone maleate is used as combination therapy.

### Combination with Metformin

A total of 670 patients with type 2 diabetes participated in two 26-week, randomized, double-blind, placebo/active-controlled studies designed to assess the efficacy of rosiglitazone maleate in combination with metformin. rosiglitazone maleate, administered in either once daily or twice daily dosing regimens, was added to the therapy of patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin.

In one study, patients inadequately controlled on 2.5 grams/day of metformin (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive 4 mg of rosiglitazone maleate once daily, 8 mg of rosiglitazone maleate once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of metformin and 4 mg of rosiglitazone maleate once daily and 8 mg of rosiglitazone maleate once daily, versus patients continued on metformin alone (Table 10).

Table 10. Glycemic Parameters in a 26-Week Combination Study of Rosiglitazone Maleate Plus Metformin

	<b>Metformin</b>	<b>Rosiglitazone Maleate 4 mg once daily + metformin</b>	<b>Rosiglitazone Maleate 8 mg once daily + metformin</b>
	N = 113	N = 116	N = 110
<b>FPG (mg/dL)</b>			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
Difference from metformin alone (adjusted mean)	—	-40*	-53*
% of patients with $\geq 30$ mg/dL decrease from baseline	20%	45%	61%
<b>HbA1c (%)</b>			
Baseline (mean)	8.6	8.9	8.9

Change from baseline (mean)	0.5	-0.6	-0.8
Difference from metformin alone (adjusted mean)	—	-1.0*	-1.2*
% of patients with $\geq 0.7\%$ decrease from baseline	11%	45%	52%
* p<0.0001 compared to metformin.			

In a second 26-week study, patients with type 2 diabetes inadequately controlled on 2.5 grams/day of metformin who were randomized to receive the combination of rosiglitazone maleate 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect for HbA1c of -0.8% over metformin alone. The combination of metformin and rosiglitazone maleate resulted in lower levels of FPG and HbA1c than either agent alone.

Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with rosiglitazone maleate demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c. In this group, increases in LDL and VLDL were also seen.

#### Combination with Sulfonylurea

A total of 3,457 patients with type 2 diabetes participated in ten 24- to 26-week randomized, double-blind, placebo/active-controlled studies and one 2-year double-blind, active-controlled study in elderly patients designed to assess the efficacy and safety of rosiglitazone maleate in combination with a sulfonylurea. rosiglitazone maleate 2 mg, 4 mg, or 8 mg daily, was administered either once daily (3 studies) or in divided doses twice daily (7 studies), to patients inadequately controlled on a submaximal or maximal dose of sulfonylurea.

In these studies, the combination of rosiglitazone maleate 4 mg or 8 mg daily (administered as single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 11 shows pooled data for 8 studies in which rosiglitazone maleate added to sulfonylurea was compared to placebo plus sulfonylurea.

Table 11. Glycemic Parameters in 24- to 26-Week Combination Studies of Rosiglitazone Maleate Plus Sulfonylurea

<b>Twice Daily Divided Dosing (5 Studies)</b>	<b>Sulfonylurea</b>	<b>Rosiglitazone Maleate 2 mg twice daily + sulfonylurea</b>	<b>Sulfonylurea</b>	<b>Rosiglitazone M 4 mg twice daily + sulfonylurea</b>
	N = 397	N = 497	N = 248	N = 346
<b>FPG (mg/dL)</b>				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43



Difference from sulfonylurea alone (adjusted mean)	–	-42*	–	-53*
% of patients with $\geq 30$ mg/dL decrease from baseline	17%	49%	15%	61%
<b>HbA1c (%)</b>				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	–	-1.1*	–	-1.4*
% of patients with $\geq 0.7\%$ decrease from baseline	21%	60%	23%	75%
<b>Once Daily Dosing (3 Studies)</b>	<b>Sulfonylurea</b>	<b>rosiglitazone maleate 4 mg once daily + sulfonylurea</b>	<b>Sulfonylurea</b>	<b>rosiglitazone maleate 8 mg once daily + sulfonylurea</b>
	N = 172	N = 172	N = 173	N = 176
<b>FPG (mg/dL)</b>				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	–	-47*	–	-66*
% of patients with $\geq 30$ mg/dL decrease from baseline	17%	48%	19%	55%
<b>HbA1c (%)</b>				

Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	—	-0.9*	—	-1.4*
% of patients with $\geq 0.7\%$ decrease from baseline	11%	36%	20%	68%
* p<0.0001 compared to sulfonylurea alone.				

One of the 24- to 26-week studies included patients who were inadequately controlled on maximal doses of glyburide and switched to 4 mg of rosiglitazone maleate daily as monotherapy; in this group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

In a 2-year double-blind study, elderly patients (aged 59 to 89 years) on half-maximal sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of rosiglitazone maleate (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110), to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and 7.72%, respectively, for the rosiglitazone maleate plus glipizide arm and 159 mg/dL and 7.65%, respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG  $\geq 180$  mg/dL) occurred in a significantly lower proportion of patients (2%) on rosiglitazone maleate plus glipizide compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on combination therapy completed the 2 years of therapy while only 51% completed on glipizide monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year study period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for HbA1c compared to no change on the glipizide arm.

### 14.3 Combination With Sulfonylurea Plus Metformin

In two 24- to 26-week, double-blind, placebo-controlled, studies designed to assess the efficacy and safety of rosiglitazone maleate in combination with sulfonylurea plus metformin, rosiglitazone maleate 4 mg or 8 mg daily, was administered in divided doses twice daily, to patients inadequately controlled on submaximal (10 mg) and maximal (20 mg) doses of glyburide and maximal dose of metformin (2 g/day). A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of sulfonylurea plus metformin and 4 mg of rosiglitazone maleate and 8 mg of rosiglitazone maleate versus patients continued on sulfonylurea plus metformin, as shown in Table 12.

Table 12. Glycemic Parameters in a 26-Week Combination Study of Rosiglitazone Maleate Plus Sulfonylurea and Metformin

	<b>Sulfonylurea + metformin</b>	<b>Rosiglitazone maleate 2 mg twice daily + sulfonylurea + metformin</b>	<b>Rosiglitazone maleate 4 mg twice daily + sulfonylurea + metformin</b>
	N = 273	N = 276	N = 277
<b>FPG (mg/dL)</b>			
Baseline (mean)	189	190	192
Change from baseline (mean)	14	-19	-40
Difference from sulfonylurea plus metformin (adjusted mean)	—	-30*	-52*

% of patients with $\geq 30$ mg/dL decrease from baseline	16%	46%	62%
<b>HbA1c (%)</b>			
Baseline (mean)	8.7	8.6	8.7
Change from baseline (mean)	0.2	-0.4	-0.9
Difference from sulfonylurea plus metformin (adjusted mean)	–	-0.6*	-1.1*
% of patients with $\geq 0.7\%$ decrease from baseline	16%	39%	63%
* p<0.0001 compared to placebo.			

## 15 REFERENCES

- Food and Drug Administration Briefing Document. Joint meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees. July 30, 2007.
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- Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

**Tablets:** each oval film-coated tablet contains rosiglitazone as the maleate as follows:

2 mg - Pink oval film coated tablets, engraved with W41; supplied in bottles of 30, 100 and 500

4 mg - Orange oval film coated tablets, engraved with W42; supplied in bottles of 30, 100 and 500.

8 mg - Brick-red oval film coated tablets, engraved with W43, supplied in bottles of 30, 100 and 500.

Store at 25°C (77°F); excursions 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container.

## 17 PATIENT COUNSELING INFORMATION

### 17.1 Patient Advice

Patients should be informed of the following:

- Rosiglitazone maleate is not recommended for patients with symptoms of heart failure.
- Patients with more severe heart failure (NYHA Class 3 or 4) cannot start Rosiglitazone maleate as the risks exceed any potential benefits in such patients.
- Results of a set of clinical studies suggest that treatment with Rosiglitazone Maleate is associated with an increased risk for myocardial ischemic events, such as angina or myocardial infarction (heart attack), especially in patients taking insulin or nitrates. Because this risk has not been confirmed or excluded in different long-term trials, definitive conclusions regarding this risk await completion of an adequately-designed cardiovascular outcome study.
- Rosiglitazone maleate is not recommended for patients who are taking nitrates or insulin.
- There are multiple medications available to treat type 2 diabetes, and each patient with diabetes is unique. The benefits and risks of each available diabetes medication should be taken into account when choosing a particular diabetes medication for a given patient.
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Rosiglitazone maleate or any other oral antidiabetic drug.

- Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but in maintaining the efficacy of drug therapy.
- It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. It can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of Rosiglitazone maleate.
- Blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgment of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.
- Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on Rosiglitazone maleate should immediately report these symptoms to their physician.
- Rosiglitazone maleate can be taken with or without meals.
- When using Rosiglitazone maleate in combination with other hypoglycemic agents, the risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
- Therapy with Rosiglitazone maleate, like other thiazolidinediones, may result in ovulation in some Rosiglitazone maleate/*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1 )*. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

## FDA-APPROVED MEDICATION GUIDE

See separate leaflet.

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### MEDICATION GUIDE

#### Rosiglitazone Maleate Tablets

Read this Medication Guide carefully before you start taking rosiglitazone maleate and each time you get a refill. There may be new information. This information rosiglitazone maleate, ask your doctor or pharmacist.

#### **What is the most important information I should know about rosiglitazone maleate tablets?**

Rosiglitazone maleate tablets can cause serious side effects, including:

##### **New or worse heart failure**

- Rosiglitazone maleate can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start on Rosiglitazone maleate.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, Rosiglitazone maleate may not be right for you.

Call your doctor right away if you have any of the following:

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- feel unusually tired

##### **Other heart problems**

Rosiglitazone maleate may increase the risk of heart problems related to reduced blood flow to the heart. These include possible increases in the risk of heart-related chest pain (angina) or "heart attack" (myocardial infarction). This risk seems to be higher in patients who took Rosiglitazone maleate with insulin or with nitrate medicines. Most people who take insulin or nitrate medicines should not also take Rosiglitazone maleate.

- If you have chest pain or a feeling of chest pressure, get medical help right away, no matter what diabetes medicines you are taking.
- Patients with diabetes have a greater risk for heart problems. It is important to work with your doctor to manage other conditions, such as high blood pressure or high cholesterol.

Rosiglitazone maleate can have other serious side effects. Be sure to read the section below “What are possible side effects of Rosiglitazone maleate?”.

### **What is Rosiglitazone maleate?**

Rosiglitazone maleate is a prescription medicine used with diet and exercise to treat adults with type 2 (“adult-onset” or “non-insulin dependent”) diabetes mellitus (“high blood sugar”). Rosiglitazone maleate helps to control high blood sugar. Rosiglitazone maleate may be used alone or with other diabetes medicines. Rosiglitazone maleate can help your body respond better to insulin made in your body. Rosiglitazone maleate does not cause your body to make more insulin. Rosiglitazone maleate can also cause serious side effects.

- In order for Rosiglitazone maleate to work best, it is very important to exercise, lose extra weight, and follow the diet recommended by your doctor.
- Rosiglitazone maleate has not been studied enough in children under 18 years of age to know if it is safe or effective in children.
- Rosiglitazone maleate is not for patients with type 1 diabetes mellitus or to treat a condition called diabetic ketoacidosis.

### **Who should not take Rosiglitazone maleate?**

Many patients with heart failure should not start taking Rosiglitazone maleate. See “What should I tell my doctor before taking Rosiglitazone maleate?”.

### **What should I tell my doctor before taking Rosiglitazone maleate?**

Before starting Rosiglitazone maleate, ask your doctor about what the choices are for diabetes medicines, and what the expected benefits and possible risks are for you in particular.

Before taking Rosiglitazone maleate, tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure.**
- **have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking Rosiglitazone maleate and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**
- **are pregnant or plan to become pregnant.** Rosiglitazone maleate should not be used during pregnancy. It is not known if Rosiglitazone maleate can harm your unborn baby. You and your doctor should talk about the best way to control your diabetes during pregnancy. If you are a premenopausal woman (before the “change of life”) who does not have regular monthly periods, Rosiglitazone maleate may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking Rosiglitazone maleate. Tell your doctor right away if you become pregnant while taking Rosiglitazone maleate.
- **are breast-feeding or planning to breast-feed.** It is not known if Rosiglitazone maleate passes into breast milk. You should not use Rosiglitazone maleate while breastfeeding.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. Rosiglitazone maleate and certain other medicines can affect each other and lead to serious side effects including high or low blood sugar, or heart problems. Especially tell your doctor if you take:

- **insulin.**
- **nitrate medicines** such as nitroglycerin or isosorbide to treat a type of chest pain called angina.
- **any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.**

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist before you start a new medicine. They will tell you if it is alright to take Rosiglitazone maleate with other medicines.

### **How should I take Rosiglitazone maleate?**

- Take Rosiglitazone maleate exactly as prescribed. Your doctor will tell you how many tablets to take and how often. The usual daily starting dose is 4 mg a day taken one time each day or 2 mg taken two times each day. Your doctor may need to adjust your dose until your blood sugar is better controlled.
- Rosiglitazone maleate may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled.
- Take Rosiglitazone maleate with or without food.

- It can take 2 weeks for Rosiglitazone maleate to start lowering blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of Rosiglitazone maleate, take it as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take double doses to make up for a missed dose.
- If you take too much Rosiglitazone maleate, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose extra weight, and get regular exercise while taking Rosiglitazone maleate.
- Your doctor should do blood tests to check your liver before you start Rosiglitazone maleate and during treatment as needed. Your doctor should also do regular blood sugar tests (for example, “A1C”) to monitor your response to Rosiglitazone maleate.
- Your doctor should check your eyes regularly. Some patients have had vision changes due to swelling in the back of the eye, called macular edema, while taking Rosiglitazone maleate.

### **What are possible side effects of Rosiglitazone maleate?**

#### **Rosiglitazone maleate can cause serious side effects including:**

- **New or worse heart failure.** See “What is the most important information I should know about Rosiglitazone maleate?”.
- **Other heart problems.** Rosiglitazone maleate may increase the risk of heart problems related to reduced blood flow to the heart. These include possible increases in the risk of heart-related chest pain (angina) or “heart attack” (myocardial infarction). See “What is the most important information I should know about Rosiglitazone maleate?”.
- **Swelling (edema).** Rosiglitazone maleate can cause swelling due to fluid retention. See “What is the most important information I should know about Rosiglitazone maleate?”.
- **Weight gain.** Rosiglitazone maleate can cause weight gain that may be due to fluid retention or extra body fat. Weight gain can be a serious problem for people with certain conditions including heart problems. See “What is the most important information I should know about Rosiglitazone maleate?”.
- **Liver problems.** It is important for your liver to be working normally when you take Rosiglitazone maleate. Your doctor should do blood tests to check your liver before you start taking Rosiglitazone maleate and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes.
- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision.
- **Fractures**, usually in the hand, upper arm or foot, in females. Talk to your doctor for advice on how to keep your bones healthy.
- **Low red blood cell count (anemia).**
- **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or hunger may mean that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy. Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy. See “What should I tell my doctor before taking Rosiglitazone maleate?”.

The most common side effects of Rosiglitazone maleate reported in clinical trials included cold-like symptoms and headache. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store Rosiglitazone maleate?**

- Store Rosiglitazone maleate at room temperature, 59° to 86°F (15° to 30°C). Keep Rosiglitazone maleate in the container it comes in.
- Safely, throw away Rosiglitazone maleate that is out of date or no longer needed.
- Keep Rosiglitazone maleate and all medicines out of the reach of children.

#### **General information about Rosiglitazone maleate**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Rosiglitazone maleate for a condition for which it was not prescribed. Do not give Rosiglitazone maleate to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes important information about rosiglitazone maleate tablets. If you would like more information about rosiglitazone maleate tablets that is written for healthcare professionals. You can also find out more about rosiglitazone maleate tablets by calling West-ward Pharmaceutical Corp at 732-542-1191.

#### **What are the ingredients in Rosiglitazone maleate?**

Active Ingredient: Rosiglitazone maleate.

Inactive Ingredients: Lactose monohydrate, lechithin, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3350, polyvinyl alcohol, red iron oxide, sodium starch glycolate type A, talc, titanium dioxide. The 4 mg tablet also contains FD&C yellow No. 6 aluminum lake and yellow iron oxide.

Always check to make sure that the medicine you are taking is the correct one. Rosiglitazone maleate tablets look like this:

2 mg – Pink oval film coated tablets, engraved with W41.

4 mg – Orange oval film coated tablets, engraved with W42.

8 mg – Brick red oval film coated tablets, engraved with W43.

REZULIN is a registered trademark of Parke-Davis Pharmaceuticals Ltd.

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

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Revised: April 2009

Revised: 07/2009

Distributed by: West-ward Pharmaceutical Corp